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(54) Title: TOPICAL VETERINARY COMPOSITIONS AND METHODS FOR THE TREATMENT AND PREVENTION OF INFECTION

(57) Abstract: The present invention provides compositions and methods for the treatment of infection in a subject. More particularly, the invention provides a therapy for the treatment or prevention of mammary infections, such as bovine mastitis, comprising the topical administration to a subject of an anti-microbial agent and a phospholipid-containing skin conditioner.



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TOPICAL VETERINARY COMPOSITIONS AND METHODS FOR THE TREATMENT AND PREVENTION OF INFECTION

Field of the Invention

[0001] The present invention provides compositions and methods for the treatment and prevention of infection. The invention is directed toward a therapy for the treatment or prevention of mammary infections, such as bovine mastitis, comprising the administration to a subject of a topical veterinary composition comprising an anti-microbial agent and a skin conditioner.

Background of the Invention

[0002] The spread of bacterial infection in connection with cow teats during the milking process results in the spread of the infectious mammary disease known as mastitis. Bovine mastitis is an inflammation of the udder. The characteristic features of inflammation are swelling, heat, redness, pain, and disturbed function. This condition, which is almost exclusively initiated by pathogenic microorganisms that have entered the teat canal after the milking process, occludes milk flow and production, decreases milk value, and may permanently impair an animal's ability to produce milk. More than 80 species of microorganisms have been identified as causal agents, although approximately 95% of mastitis is believed to be caused by four pathogens: staphylococcus aureus, streptococcus agalactiae, streptococcus dysagalactiae, and streptococcus uberis. Mastitis-causing pathogens fall into two categories, namely, contagious and environmental. Contagious bacteria, such as streptococcus agalactiae and staphylococcus aureus, primarily colonize host tissue sites such as mammary glands, teat canals, and teat skin lesions; and are spread from one infected cow to another during the milking process. Environmental bacteria, often streptococci, enterococci, and coliform organisms, are commonly present

within the cow's surroundings from sources such as cow feces, soil, plant material, bedding, or water; and infect by casual opportunistic contact with an animal.

[0003] The distinction between contagious and environmental pathogens, although not exclusive, is of practical importance because different dairy herd maintenance measures are needed for the different groups of microorganisms. In all bovine mastitis cases, whatever the causal microorganism, the route of transmission of the invading pathogen into the inner gland of the udder is through the teat orifice and teat canal. The common sources of harmful microorganisms include unsanitary milking equipment, the milker, other mastitic animals, an unsanitary stable environment, and the animals' own elimination (defecation/urination) processes.

[0004] A 1996 study by the National Mastitis Council (NMC) estimated annual monetary losses per cow due to mastitis at \$184.40 totaling to an extrapolated average of \$1.7 billion in the U.S. alone (Crist, W.L. et al., (1997) Mastitis and Its Control, University of Kentucky Extension Service - College of Agriculture). The spread of this disease is generally reduced by the use of antimicrobial compositions; for example, antimicrobial teat dips containing iodine have been shown to be effective against mammary infections and mastitis-causing bacteria (Pankey, J.W. et al., (1983) J. Dairy Sci. 66 (1), 161-167). These compositions are usually administered to the teat by dipping or spraying the teat prior to milking as well as after removal of the milking cup. To reduce mastitis, commercial teat dips have been developed containing a variety of antimicrobial agents including iodophors, quaternary ammonium compounds, chlorine release compounds (e.g. alkali hypochlorites), oxidizing compounds (e.g. hydrogen peroxide, peracids), protonated carboxylic acids (e.g. heptanoic, octanoic, nonanoic, decanoic, undecanoic acids), acid anionics

(e.g. alkylaryl sulfonic acids), chlorine dioxide (from chlorite), and bisbiguanides such as chlorhexidine. These agents, which have varying degrees of effectiveness, limit the transmission of mastitis by reducing pathogen populations on the teat. However, there are problems associated with the use of antimicrobials. The most prevalent are irritation to the teat and teat cracking. To alleviate these problems, emollient additives such as glycerin and lanolin have been included in such compositions. However, even with the use of these emollients skin irritation can still occur.

[0005] The NMC not only stresses the importance of proper teat sanitation, but also proper teat care for the prevention of mastitis. The economic harm caused by mastitis has led to much research in its control. Physical stresses as well as environmental conditions have been reported to be large contributors to mastitis infection (See U.S. Patent: 20020051789). Since it was documented that sub-clinical mastitis was directly related to poor teat condition (Neijenhuis, F. et al., (2001) J. Dairy Sci. (84) 2664-2672), a number of commercial teat dip solutions incorporating conditioning agents have evolved (National Mastitis Council, Summary of Peer-Reviewed Publications on Efficacy of Premilking and Postmilking Teat Disinfectants Published Since 1980; Jan. 2002). Recently, teat end callosity and roughness have been shown to have a direct relationship with clinical mastitis (Neijenhuis, F. et al., (2001) J. Dairy Sci. (84) 2664-2672). The reduction of chapping and irritation of teats as well as keeping the teat flexible is very important in controlling mammary infections. Currently, glycerin is often used as a teat conditioner in teat dip solutions. However, studies indicate no significant decrease in mastitis-causing bacteria such as staphylococcus aureus, streptococcus agalactiae, or coliforms when the glycerin content is increased from 2% to 10% in a 1% iodine teat dip solution

(National Mastitis Council, Summary of Peer-Reviewed Publications on Efficacy of Premilking and Postmilking Teat Disinfectants Published Since 1980; Jan. 2002).

[0006] Thus, although many teat dip products are available, there is a continuing need for new and effective teat dip compositions having immediate and long lasting antimicrobial effect against a wide spectrum of mastitis-causing organisms that also aid in overall skin condition of the teat.

Summary of the Invention

[0007] Among the several aspects of the present invention is to provide a method and a composition for the treatment and prevention of mammary infections in a subject. The composition comprises an anti-microbial agent and a phospholipid-containing skin conditioner, and the method comprises administering to a subject a topical veterinary composition comprising an anti-microbial agent and a phospholipid-containing skin conditioner.

[0008] Another aspect of the invention is to provide such compositions and methods that do not chap, peel, or irritate the subject's skin.

[0009] In one embodiment, the composition comprises the anti-microbial agent iodine, and the phospholipid linoleamidopropyl phosphatidylglycerol dimonium chloride phosphate.

[0010] Other aspects of the invention are described in more detail below.

Abbreviations and Definitions

[0011] Where used, either alone or within other terms such as "haloalkyl," "alkylsulfonyl," "alkoxyalkyl," and "hydroxyalkyl," the term "alkyl" is a linear, cyclic, or branched radical having one to about twenty carbon atoms or,

preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, and the like.

[0012] The term "alkylamino" is an amino group that has been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino, or the like.

[0013] The term "aryl," alone or in combination, is a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as benzyl, phenyl, naphthyl, tetrahydronaphthyl, indane, and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxy-carbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxy-carbonyl, and aralkoxy-carbonyl.

[0014] When used in combination, for example "alkylaryl" or "arylalkyl," the individual terms listed above have the meaning indicated above.

[0015] The description "concentrate" is in reference to the phrase "teat sanitizer concentrate" in which the diluent of a ready-to-use teat sanitizer is removed during manufacture and diluent is re-added at the convenience of the user. In addition, it is not a requirement that the diluent re-added

has to match the diluent removed - only a diluent compatible with the concentrated mixture is required.

[0016] The term "emollient" refers to an agent that softens or soothes the skin. Emollients typically act as a replenisher of oils and fats to the skin; but, an emollient may promote the retention of moisture in skin while achieving a softening or soothing effect.

[0017] The term "humectant" refers to a substance that promotes retention of moisture; and, in particular to this embodiment, the retention of moisture in skin. Humectants do not directly soften and soothe skin, but allow the skin to retain its natural moisture.

[0018] The term "subject" for purposes of treatment includes any lactating animal. The subject can be a domestic livestock species, a laboratory animal species, a zoo animal, or a companion animal. In one embodiment, the subject is a cow.

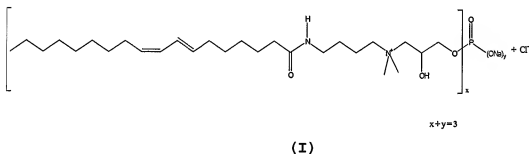
[0019] The phrase "therapeutically effective" is intended to qualify the amount of the topical veterinary composition comprising an antimicrobial agent and a phospholipid-containing skin conditioner, which will achieve the goal of improvement in disorder severity and the frequency of incidence over no treatment.

Description of the Preferred Embodiments

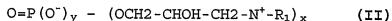
[0020] The present invention provides a therapy comprising the administration to a subject of a therapeutically effective amount of a topical veterinary composition comprising an anti-microbial agent and a phospholipid-containing skin conditioner. The therapy is used to treat or prevent infection, for example, mammary infections such as bovine mastitis.

Phospholipids

[0021] A number of suitable phospholipids may be employed in the composition of the current invention. Suitable phospholipids act as skin conditioners and prevent chapping, peeling, and irritation of the skin. In addition, suitable phospholipids will aid in the flexibility of the skin. In one embodiment, the composition contains, for example, the phospholipid *cis*-9, *trans*-11-octadecanamidopropyl phosphatidylglycerol phosphate, Formula I.



[0022] In another embodiment, the composition contains a phospholipid represented by Formula II.



[0023] wherein $x + y = 3$ or mixtures thereof; and

[0024] wherein R_1 is selected from the group consisting of alkyl, alkylamides, and organosilicone modified alkyl or alkylamides which contain between 8 and 25 carbon atoms or mixtures thereof.

[0025] This typically describes diesters or triester phosphatides consisting of a glycerol or triglyceride, one to three fatty acids or natural oils, and a hydrophilic phosphorylated group, and of the general structure: (fatty acid) $_2$ - glycerol - phosphorylated group or (fatty acid) $_3$ - triglyceride - phosphorylated group and their organosilicone modified counterparts. The fatty acid preferred is linoleic,

an unsaturated fatty acid derived from safflower oil, but any unsaturated fatty acid such as lauroleic, myristoleic, linolenic, eleostearic, licanic, and arachadinic and their corresponding isomers or any natural oil such as coconut, olive, palm, or castor oil, or, any combination of a natural oil and an unsaturated fatty acid may be substituted. Synthetic phospholipid alternatives to the natural derived oils and fatty acids are commercially abundant and do not interfere with the general function of the phospholipid.

[0026] In one embodiment, the ratio of phospholipid to antimicrobial agent is between about 0.1:1 and about 10:1. Unless otherwise stated, all ratios and percentages listed herein are by weight; and, unless otherwise stated, refer to ready-to-use compositions.

[0027] In a further embodiment, the ratio of phospholipid to antimicrobial agent is between about 1:1 and about 4:1.

[0028] In still further embodiment, the ratio of phospholipid to antimicrobial agent is between about 1.5:1 and about 2.5:1, between about 1.75:1 and about 2.25:1, or about 2:1.

[0029] As a general proposition, the phospholipid concentration is between about 0.01 and about 20 percent of the overall composition. In a preferred embodiment, phospholipid constitutes between about 0.9 and about 1.1 percent of the overall composition. In another preferred embodiment, the phospholipid constitutes between about 1.9 and 2.1 percent of the overall composition. In still a further preferred embodiment, the phospholipid constitutes between about 3.9 and 4.1 percent. The composition is provided as a ready-to-use formula having the foregoing phospholipid concentrations, or is provided as a concentrate to be diluted. When the composition is provided as a concentrate having a lesser concentration of the diluent than the ready-to-use formula, the phospholipid concentration is proportionally

greater such that it provides the desired final concentration after being diluted by the user or supplier.

[0030] In another embodiment, compounds that are useful as a phospholipid in connection with the compositions and methods of the present invention, include, but are not limited to:

[0031] linoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Arasilk EFA and Colalipid SAFL;

[0032] cocoamidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Arasilk CDM and Colalipid C;

[0033] sunfloweramidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Colalipid SUN;

[0034] sodium olivamidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Colalipid OL;

[0035] stearamidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Arasilk SV and Colalipid ST;

[0036] ricinoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Colalipid RC;

[0037] di-linoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Colalipid DLO;

[0038] poly(ethylene glycol)_{n=8} dimethicone sunfloweramidopropyl phosphatidylglycerol dimonium chloride phosphate complex, marketed under the trade name Colalipid SIL;

[0039] dimethicone saffloweramidopropyl phosphatidylglycerol dimonium chloride phosphate complex, marketed under the trade name Arasilk PLN;

[0040] sodium grapeseedamidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Colalipid GS; and

[0041] sodium borageamidopropyl phosphatidylglycerol dimonium chloride phosphate, marketed under the trade name Arasilk GLA.

Antimicrobial Agents

[0042] A number of suitable antimicrobial agents are employed in the compositions of the present invention. The criteria employed in selecting an antimicrobial agent include low skin irritancy, water solubility, and effectiveness against pathogens such as staphylococcus aureus, streptococcus agalactiae, streptococcus dysagalactiae, and streptococcus uberis. In one embodiment, the antimicrobial agent is iodophor. In another embodiment, the antimicrobial agent is a quaternary ammonium compound. In yet another embodiment, the antimicrobial agent is a chlorine release compound such as alkali hypochlorite. In still another embodiment, the antimicrobial agent is hydrogen peroxide. In a further embodiment, the antimicrobial agent is a protonated carboxylic acid (e.g. heptanoic, octanoic, nonanoic, decanoic, undecanoic, capric, lauric, myristic, palmitic, stearic, oleic, linoleic, and linolenic acid and their corresponding isomers). In a still further embodiment, the antimicrobial agent is an alkylaryl sulfonic acid. In another embodiment, the antimicrobial agent is chlorine dioxide. In yet another embodiment, the antimicrobial agent is chlorhexidine.

[0043] As a general proposition, the concentration of the anti-microbial agent in the composition varies depending upon the specific agent selected. In one preferred embodiment the anti-microbial agent is iodine. In one embodiment the concentration of iodine is between about 0.1 and about 2.0 percent of the overall composition. When the composition is provided as a concentrate having a lesser concentration of the

diluent than the ready-to-use formula, the iodophor or other anti-microbial agent concentration is proportionally greater such that it provides the desired final concentration after being diluted by the user or supplier.

Other Agents

[0044] The compositions of the present invention are preferably prepared with the incorporation of a chemical agent or agents that have an emollient activity on the skin. Anhydrous oil systems and water-in-oil systems are not preferred in the present invention, due to the fact that residual oil can promote adhesion of waste particulate matter and compromise the antimicrobial effectiveness of the composition. Therefore, oil-in-water compositions are preferred in the present compositions. The preferred emollient system for the compositions of the present invention also includes a water-soluble refatting agent. One preferred emollient for the compositions of the present invention is a phospholipid in combination with glycerin. The total concentration of the emollient and re-fatting agents in the antimicrobial compositions is generally about 0 to about 25 percent (all percentages herein are by weight), more preferably about 2 to about 15 percent, and even more preferably about 4 to about 6 percent; and, increases proportionally when used in the form of a concentrate as the diluent is removed.

[0045] Other adjuvants, such as pH adjustors and buffering agents, can be blended with the compositions of the present invention. Useful pH adjustors can be either organic or inorganic acids or bases, alone or in combination with their respective salts. Preferred buffering agents include, for example, citric acid, sorbic acid, ascorbic acid, malic acid, and succinic acid. Preferred basifying agents include, for example, triethanolamine, ammonium hydroxide, potassium

hydroxide, and sodium hydroxide. The pH adjustors, when present, are used in sufficient quantities to bring the pH of the composition into the desired range, generally from about pH 4 to about pH 6. Other adjuvants can include defoamers, such as dimethicone and dicyclomethicone; emollients, such as oleyl alcohol, oleyl lanolate, and lanolin; humectants such as propylene glycol and sorbitol; and nutrients, such as vitamin E (alpha tocopherol). In addition, optional ingredients may include both water and oil-soluble vitamins and wound-healing agents (e.g., proteins, lipids, nucleic acids, etcetera).

[0046] The compositions of the present invention can also optionally include stabilizers and thickening agents to achieve viscosities within a useful range appropriate for the mode of application. Such agents include hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, carboxy methyl cellulose, emulsifying waxes, alkyl triammonium methosulfate, and ceteraryl octanoate. When used, the total concentration of the stabilizers and thickening agents in compositions of the present invention are generally about 0 to about 2 percent, more preferably at least about 0.01 to about 0.75 percent, and even more preferably about 0.3 to about 0.6 percent. Formulations wherein the total concentration of the stabilizers and thickening agents is less than about 0.1 percent, and preferably not more than about 0.05 percent, can be utilized. When the composition is provided as a concentrate having a lesser concentration of the diluent than the ready-to-use formula, the stabilizer and thickening agent concentration is proportionally greater such that it provides the desired final concentration after being diluted by the user or supplier. Although the compositions are aqueous based, certain ingredients may require the presence of a more lipophilic solvent for proper stabilization. Preferred additional solvents are polyhydric alcohol solvents, or "polyol" solvents, such as the polyalkylene glycols having

alkylene moieties containing about 2-3 carbon atoms, preferably the polyethylene glycols. Molecular weight ranges of from about 200-4000 are preferred for the polyalkylene glycols (e.g., propylene glycol). These polyol solvents are useful as a humectant and serve to help solubilize the lipophilic compounds.

[0047] Generally speaking, the compositions of the present invention are preferably administered to the subject immediately prior to the milking process as well as immediately after the completion of the milking process.

Field Studies

[0048] Tables T1 - T5 depict results attained from various field studies as described below, wherein:

[0049] composition "A" is a commercially available teat dip that contains 0.5 % iodine and 74% emollients;

[0050] composition "B" is a composition of the present invention comprising 0.5% iodine and 1.0% phospholipid and 0% added emollient;

[0051] composition "C" is a commercially available teat dip that contains 1.0% iodine and 10.0% emollients;

[0052] composition "D" is a composition of the present invention comprising 0.5% iodine and 1.0% phospholipid with 5% added emollient; and

[0053] composition "E" is a composition of the present invention comprising 1.0% iodine and 1.0% phospholipid with 5% added emollient.

[0054] Table T1 lists the quantity and qualities of the milk obtained from a 30 day study of cows who have birthed once (primiparous) and those who have birthed more than once (multiparous) for a commercially available teat dip that contains 0.5 % iodine with 74% emollients (A) and a composition of the present invention comprising 0.5% iodine

and 1.0% phospholipid with 0% added emollient (B). The treatment P value indicates that the only statistical significance between the two products is the fat percent and MUN value.

Table T1 (Effect of teat dip on milk yield and composition)

Item ¹	Primiparous		Multiparous		Treatment	P value	
	A	B	A	B		Parity	Treat *Parity
N	23	25	44	41			
Milk, kg/day	40.9	43.3	41.0	41.6	0.8970	0.1925	0.1683
ECM, kg/day	41.3	41.3	40.9	42.6	0.6759	0.5901	0.3028
Fat, %	3.64	3.46	3.40	3.53	0.0530	0.3207	0.0530
Protein, %	3.09	3.20	3.14	3.13	0.1490	0.6482	0.0018
Lactose, %	4.95	5.00	4.95	4.94	0.3224	0.0955	0.0730
SNF, %	8.97	9.17	8.99	9.02	0.6567	0.0352	0.0003
MUN, mg/dL	16.23	16.48	16.73	16.66	0.0278	0.0545	0.3713
Fat, kg/day	1.44	1.38	1.41	1.50	0.3319	0.3214	0.1081
Protein, kg/day	1.26	1.38	1.28	1.29	0.5450	0.1621	0.0071
Lactose, kg/day	2.03	2.17	2.04	2.06	0.6728	0.1245	0.0782

¹Values have been adjusted for covariate

[0055] Table T2 scores the teat and teat-end condition following a 30 day study of primiparous and multiparous cows for a commercially available teat dip that contains 0.5 % iodine and 74% emollients (A) and a composition of the present invention comprising 0.5% iodine and 1.0% phospholipid with 0% added emollient (B). The treatment P value indicates that there is no statistical significance between the two products.

Table T2 (Effect of teat dip on teat condition and teat ends)

Item ¹	Primiparous		Multiparous		Treatment	P value	
	A	B	A	B		Parity	Treat *Parity
N	21	26	45	46			
Left front	1.81	2.04	2.04	1.97	0.5125	0.5338	0.2297
Right front	1.73	2.07	1.93	1.91	0.1853	0.8715	0.1489
Left rear	1.39	1.57	1.59	1.56	0.4575	0.3587	0.3251
Right rear	1.42	1.78	1.69	1.56	0.2767	0.8196	0.0322
Left front end	2.59	2.45	2.75	2.81	0.6336	0.0046	0.2145
Right front end	2.63	2.59	2.86	2.82	0.6403	0.0150	0.9540
Left rear end	2.27	2.33	2.55	2.53	0.8327	0.0074	0.6287
Right rear end	2.48	2.33	2.52	2.49	0.3155	0.2907	0.5563

¹Values have been adjusted for covariate

Table T3 compares the somatic cell count (SCC) following a 30 day study of primiparous and multiparous cows for a commercially available teat dip that contains 0.5 % iodine and 74% emollients (A) and a composition of the present invention comprising 0.5% iodine and 1.0% phospholipid with 0% added emollient (B). The treatment P value indicates that there is no statistical significance between the two products.

Table T3 (Effect of teat dip on somatic cell count)

Item ¹	Primiparous		Multiparous		Treatment	P value	
	A	B	A	B		Parity	Treat *Parity
N	23	25	45	43			
SCC X 1000 ^a	79	123	250	355	0.3893	0.0200	0.7195
N	23	25	44	41			
SCC x 1000 ^b	49	58	122	135	0.5947	0.0005	0.9220
N	23	25	44	41			
SCC x 1000 ^c	52	62	126	138	0.6034	0.0004	0.9422

¹Values have been adjusted for covariate^aAll values used in analysis^bValues above 800,000 SCC removed^cValues above 998,000 SCC removed

Table T4 lists the quantity and qualities of the milk obtained from a six week study of primiparous and multiparous cows for a commercially available teat dip that contains 1.0 % iodine and 10% emollients (C), a composition of the present invention comprising 0.5% iodine and 1.0% phospholipid with 5% added emollient (D), and a composition of the present invention comprising 1.0% iodine and 1.0% phospholipid with 5% added emollient (E). The treatment P value indicates that the only statistical significance between the two products are the ECM (energy corrected milk), lactose, and SNF (solids not fat).

Table T4 (Effect of teat dip on milk yield and composition)

Item ¹	Primiparous			Multiparous			P value		
	C	D	E	C	D	E	T	P	T*P
N	15	16	13	19	21	20			
Milk, kg/day	36.9	36.6	38.4	36.8	35.2	37.6	0.511	0.2032	0.6624
ECM, kg/day	37.3	37.5	38.7	36.2	35.6	38.0	0.0218	0.0655	0.7578
Fat, %	3.62	3.72	3.50	3.41	3.48	3.56	0.9815	0.0664	0.1756
Protein, %	3.15	3.10	3.15	3.14	3.17	3.15	0.0507	0.2834	0.1764
Lactose, %	4.99	4.93	4.99	4.90	4.93	4.93	0.0287	0.0148	0.1666
SNF, %	9.08	8.95	9.05	8.96	9.03	9.01	0.0047	0.4350	0.0246
MUN, mg/dL	17.61	16.66	17.27	16.75	16.72	17.31	0.1316	0.3325	0.2546
Fat, kg/day	1.31	1.35	1.33	1.23	1.25	1.33	0.0576	0.0780	0.4628
Protein, kg/day	1.15	1.13	1.20	1.14	1.10	1.78	0.2724	0.2675	0.9545
Lactose, kg/day	1.84	1.81	1.92	1.81	1.74	1.86	0.0915	0.1166	0.9228

¹Values have been adjusted for covariate

Table T5 compares the somatic cell count (SCC) following a six week study of primiparous and multiparous cows for a commercially available teat dip that contains 1.0 % iodine and 10% emollient (C), a composition of the present invention comprising 0.5% iodine and 1.0% phospholipid with 5% added emollient (D), and a composition of the present invention comprising 1.0% iodine and 1.0% phospholipid with 5% added emollient (E). The treatment P value indicates that there is no statistical difference between the two products.

Table T5 (Effect of teat dip on somatic cell count)

Item ¹	Primiparous			Multiparous			P value		
	C	D	E	C	D	E	T	P	T*P
N	15	16	13	19	21	20			
SCC x 1000 ^a	293	274	585	428	322	221	0.6659	0.5354	0.0911
N	15	16	13	19	21	20			
SCC x 1000 ^b	115	74	124	215	168	139	0.4245	0.0196	0.4401
N	15	16	13	19	21	20			
SCC x 1000 ^c	123	69	132	226	198	191	0.5851	0.0052	0.6955

¹Covariate used for adjustment^aAll values used in analysis - SCC2 x treat, SCC2 x parity, SCC2 x treat x parity interaction^bValues above 800,000 SCC removed - SCC2 x treat, SCC2 x treat x parity interaction^cValues above 998,000 SCC removed - SCC2 x treat, SCC2 x treat x parity interaction**Examples**

[0056] Examples 1 - 6 describe formulas for a topical veterinary composition comprising an anti-microbial agent and a phospholipid-containing skin conditioner.

Generalized Ready-to-Use Teat Sanitizer:

[0057] A ready-to-use iodine teat sanitizer containing 1) a thickening agent such as an alkyl-hydroxy cellulose, 2) a synthetic surfactant such as an alkyl-aryl poly(ethoxy) ethanol or an n-alkyl poly(ethoxy) ethanol for detergency, wetting, and stability, 3) glycerin as an emollient, 4) a phosphate ester surfactant for added stability, 5) a phospholipid for enhanced teat conditioning, 6) an organic acid such as citric acid as a buffer, 7) a 20% iodine concentrate pre-manufactured by West Agro, and 8) a metal hydroxide for use as a pH neutralizer with the balance of ingredients being water. The solution is manufactured at ambient temperatures, blended until homogenous, and

neutralized to a final pH between 4.8 and 5.2 for optimal free iodine:

- a) where 2.00 - 35.00% is used of an alkyl-aryl poly(ethoxy) ethanol and/or an n-alkyl poly(ethoxy) ethanol where the alkyl moiety ranges from C7 to C14 and their degree of polymerization ranges from 7-14, with an ideal alkyl moiety of C8 or C9 and an ideal degree of polymerization of 9 or 10,
- b) where 0.00 - 0.50% is used of an alkyl-hydroxy cellulose with an alkyl moiety of C1 to C3, with an ideal alkyl moiety of C2,
- c) where 0.00 - 25.00% of glycerin is used,
- d) where 0.10 - 8.00% of an alkyl-aryl poly(ethoxy) phosphate ester is used where the alkyl moiety ranges from C7 to C14 and their degree of polymerization ranges from 2 to 6, with an ideal alkyl moiety of C8 or C9 and an ideal degree of polymerization of 4 to 6, and/or a C10 to a C18 fatty acid poly(ethoxy) phosphate ester including, but not limited to, capric, lauric, myristic, palmitic, stearic, oleic, linoleic, linolenic, and arachidonic acid and their corresponding isomers with a degree of polymerization ranging from 2 to 6, with a lauric phosphate ester as the ideal fatty acid with 3 degrees of polymerization,
- e) where 0.01 - 20% of a phospholipid is used where the fatty acid includes, but is not limited to, those acids whose carbon content ranges from C8 to C25 and preferably consists of at least one C-C double bond and no more than four C-C double bonds in their degree of unsaturation, with an ideal fatty acid carbon length of C18 and two C-C double bonds, or a natural oil such as coconut, olive, palm, or castor

- oil, or, any combination of a natural oil and an unsaturated fatty acid is preferred,
- f) where 0.50% - 29.00% of an iodine concentrate such as TDC-20 provided by West Agro, Inc. which consists of at least a 20% iodine acid suspension, and
- g) where 0.00% - 10.00% of a water soluble vitamin E (40% active) is used; however, 100% active vitamin E, or any bio-active tocopherol, may be substituted.

Example 1

[0058] Methocel J5MS (alkyl-hydroxy cellulose, 0.18 g) was added to warm water (70-75F, 87.64 g), and mixed until fully saturated. Igepal CO-720 (alkyl-aryl poly(ethoxy)ethanol, 3.00 g), glycerin (>99%, 5.00 g), Arasilk EFA (linoleic phospholipid, 1.00 g), CEDAPHOS FA-600 (phosphate ester, 0.50 g), and TDC-20 (20% iodine suspension, 2.5 g) are added and mixed with low shear until homogenous. Citric acid (0.05 g) is added and mixed thoroughly. The solution is neutralized to a pH of 4.8 to 5.2 with 50% sodium hydroxide (aq., 0.13 g). The solution in Example 1 is stable for at least one year at both ambient and elevated temperatures of 130 degrees Fahrenheit.

Example 2

[0059] Methocel J5MS (alkyl-hydroxy cellulose, 0.25 g) was added to warm water (70-75F, 90.58 g), and mixed until fully saturated. Igepal CO-720 (alkyl-aryl poly(ethoxy)ethanol, 3.00 g), glycerin (>99%, 1.99 g), Arasilk EFA (linoleic phospholipid, 1.00 g), CEDAPHOS FA-600 (phosphate ester, 0.50 g), and TDC-20 (20% iodine suspension, 2.5 g) are added and mixed with low shear until homogenous. Citric acid (0.05 g) is added and mixed thoroughly. The solution is neutralized to a pH of 4.8 to 5.2 with 50% sodium hydroxide (aq., 0.13 g). The solution in Example 2 is stable for at least one year at both ambient and elevated temperatures of 130 degrees Fahrenheit.

Example 3

[0060] To ambient water (88.25 g), Iconol NP9 (alkyl-aryl poly(ethoxy)ethanol, 3.00 g), glycerin (>99%, 2.00 g), Arasilk EFA (linoleic phospholipid, 0.10 g), CEDAPHOS FA-600 (phosphate ester, 0.50 g), and TDC-20 (20% iodine suspension, 5.0 g) are added and mixed with low shear until homogenous. Citric acid (0.05 g) is added and mixed thoroughly. The solution is neutralized to a pH of 4.8 to 5.2 with 50% sodium hydroxide (aq., 0.20 g). The solution in Example 3 is stable for at least one year at both ambient and elevated temperatures of 130 degrees Fahrenheit.

Example 4

[0061] To ambient water (85.25 g), Iconol NP9 (alkyl-aryl poly(ethoxy)ethanol, 3.00 g), glycerin (>99%, 5.00 g), Arasilk EFA (linoleic phospholipid, 1.00 g), CEDAPHOS FA-600 (phosphate ester, 0.50 g), and TDC-20 (20% iodine suspension, 5.0 g) are added and mixed with low shear until homogenous. Citric acid (0.05 g) is added and mixed thoroughly. The solution is neutralized to a pH of 4.8 to 5.2 with 50% sodium hydroxide (aq., 0.20 g). The solution in Example 4 is stable for at least one year at both ambient and elevated temperatures of 130 degrees Fahrenheit.

Generalized Teat Sanitizer Concentrate:

[0062] A concentrate of the general teat sanitizer is similarly prepared, except the amount of diluent (water) is reduced to provide a concentrate that when re-mixed with diluent prepares a ready-to-use product.

Example 5

[0063] Ambient water (1.00 g), Igepal CO-720 (alkyl-aryl poly(ethoxy)ethanol, 33.00 g), glycerin (>99%, 21.00 g), Arasilk EFA (linoleic phospholipid, 10.0 g), CEDAPHOS FA-600 (phosphate ester, 5.50 g), and TDC-20 (20% iodine suspension,

25.42 g) are all added together and mixed with low shear until homogenous. Citric acid (1.43 g) is added and mixed thoroughly. The solution is neutralized to a pH of 4.8 to 5.2 with 50% sodium hydroxide (aq., 2.65 g). The solution in Example 5 is stable for at least one year at both ambient and elevated temperatures of 130 degrees Fahrenheit. This concentrate is diluted 1 part concentrate to 10 parts water for a ready-to-use teat sanitizer.

Example 6

[0064] Ambient water (41.20 g), Iconol NP9 (alkyl-aryl poly(ethoxy)ethanol, 13.31 g), glycerin (>99%, 17.74 g), Arasilk EFA (linoleic phospholipid, 2.22 g), CEDAPHOS FA-600 (phosphate ester, 2.22 g), and TDC-20 (20% iodine suspension, 22.20 g) are all added together and mixed with low shear until homogenous. Citric acid (0.22 g) is added and mixed thoroughly. The solution is neutralized to a pH of 4.8 to 5.2 with 50% sodium hydroxide (aq., 0.89 g). The solution in Example 6 is stable for at least one year at both ambient and elevated temperatures of 130 degrees Fahrenheit. This concentrate is diluted 1 part concentrate to 3 parts water for a ready-to-use teat sanitizer.

[0065] Such preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, preservatives and/or aromatic substances and the like which do not deleteriously react with the active compounds. Typical preservatives can include potassium sorbate, sodium metabisulfite, methyl paraben, propyl paraben, thimerosal, etc.

Indications to be Treated

[0066] Generally speaking, the compositions of the present invention comprise a therapeutically effective amount

of an anti-microbial agent and a phospholipid-containing skin conditioner, employed to treat or prevent infection.

[0067] In one aspect, the invention provides a method to treat or prevent an infection caused by pathogens in or on the epidermal surface of the skin. In one embodiment, the infection is a mammary infection. In one alternative to this embodiment, the mammary infection is mastitis.

[0068] In another aspect, the invention provides a method to treat or prevent an infection caused by a fungus or virus in or on the epidermal surface of the skin.

[0069] The foregoing relates only to a limited number of embodiments that have been provided for illustration purposes only. It is intended that the scope of invention is defined by the appended claims and that modifications to the embodiments above may be made that do not depart from the scope of the invention.

What is claimed is:

1. A topical veterinary composition for the treatment or prevention of infection in animals comprising an anti-microbial agent and a phospholipid-containing skin conditioner.

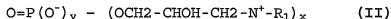
2. The composition of claim 1 wherein the anti-microbial agent is selected from the group consisting of iodine, quaternary ammonium compounds, chlorine release compounds, peroxides, protonated carboxylic acids, alkylaryl sulfonic acids, chlorine dioxide, and chlorhexidine.

3. The composition of claim 1 comprising between about 0.01 and about 20 wt % phospholipid compound.

4. The composition of claim 1 comprising between about 0.1 and about 2 wt % iodine as the anti-microbial agent.

5. The composition of claim 1 wherein the composition is a concentrate for dilution with a diluent to yield a ready-to-use composition comprising between about 0.01 and about 20 wt % phospholipid compound and between about 0.1 and 2 wt % iodine as the anti-microbial agent.

6. The composition of claim 1 wherein the phospholipid is a compound of the formula:



wherein $x + y = 3$ or mixtures thereof; and

wherein R_1 is selected from the group consisting of alkyl, alkylamides, and organosilicone modified alkyl or alkylamides which contain between 8 and 25 carbon atoms or mixtures thereof.

7. The composition of claim 1 wherein the phospholipid is selected from the group consisting of:
linoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, cocoamidopropyl phosphatidylglycerol dimonium chloride phosphate, sunfloweramidopropyl phosphatidylglycerol dimonium chloride phosphate, sodium olivamidopropyl phosphatidylglycerol dimonium chloride phosphate, stearamidopropyl phosphatidylglycerol dimonium chloride phosphate, ricinoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, di-linoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, poly(ethylene glycol)_{n=8} dimethicone sunfloweramidopropyl, phosphatidylglycerol dimonium chloride phosphate complex, dimethicone saffloweramidopropyl phosphatidylglycerol dimonium chloride phosphate complex, sodium grapeseedamidopropyl phosphatidylglycerol dimonium chloride phosphate, and sodium borageamidopropyl phosphatidylglycerol dimonium chloride phosphate.

8. The composition of claim 1 wherein the phospholipid is present in a weight ratio to the antimicrobial agent of between about 0.1:1 and about 10:1.

9. The composition of claim 1 wherein the phospholipid is present in a weight ratio to the antimicrobial agent of between about 1:1 and about 4:1.

10. The composition of claim 1 wherein the phospholipid is present in a weight ratio to the antimicrobial agent of between about 1.5:1 and about 2.5:1.

11. The composition of claim 1 wherein the phospholipid is present in a weight ratio to the antimicrobial agent of about 2:1.

12. The composition of claim 1 further comprising a phosphate ester surfactant.

13. The composition of claim 12 wherein the phosphate ester surfactant comprises an alkyl-aryl poly(ethoxy) phosphate ester.

14. The composition of claim 13 wherein the phosphate ester surfactant has an alkyl moiety in the range of C7 to C14 and a degree of polymerization in the range of 2 to 6.

15. The composition of claim 12 wherein the phosphate ester surfactant comprises a C10 to a C18 fatty acid poly(ethoxy) phosphate ester.

16. The composition of claim 12 wherein the phosphate ester surfactant is selected from the group consisting of capric, lauric, myristic, palmitic, stearic, oleic, linoleic, linolenic, and arachidonic acid and their corresponding isomers with a degree of polymerization ranging from 2 to 6.

17. The composition of claim 1 further comprising a synthetic surfactant.

18. The composition of claim 17 wherein the synthetic surfactant comprises an alkyl-aryl poly(ethoxy) ethanol.

19. The composition of claim 17 wherein the synthetic surfactant comprises an n-alkyl poly(ethoxy) ethanol.

20. The composition of claim 18 wherein the synthetic surfactant has an alkyl moiety in the range of C7 to C14 and has a degree of polymerization in the range of 7-14.

21. The composition of claim 19 wherein the synthetic surfactant has an alkyl moiety in the range of C7 to C14 and has a degree of polymerization in the range of 7-14.

22. The composition of claim 18 wherein the synthetic surfactant has an alkyl moiety in the range of C8 to C9 and has a degree of polymerization in the range of 9-10.

23. The composition of claim 19 wherein the synthetic surfactant has an alkyl moiety in the range of C8 to C9 and has a degree of polymerization in the range of 9-10.

24. The composition of claim 1 further comprising a thickening agent.

25. The composition of claim 24 wherein the thickening agent comprises an alkyl-hydroxy cellulose.

26. The composition of claim 24 wherein the thickening agent has an alkyl moiety in the range of C1 to C3.

27. The composition of claim 24 wherein the thickening agent has an alkyl moiety of C2.

28. The composition of claim 1 further comprising any bioactive tocopherol.

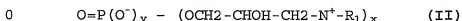
29. The composition of claim 28 wherein the bioactive tocopherol is vitamin E.

30. A veterinary composition for treating or preventing bovine mastitis comprising:

a phospholipid-containing skin conditioner; and

an anti-microbial agent selected from the group consisting of iodine, quaternary ammonium compounds, chlorine release compounds, peroxides, protonated carboxylic acids, alkylaryl sulfonic acids, chlorine dioxide, and chlorhexidine.

31. The composition of claim 30 wherein the phospholipid has the formula:



wherein $x + y = 3$ or mixtures thereof; and

wherein R_1 is selected from the group consisting of alkyl, alkylamides, and organosilicone modified alkyl or alkylamides which contain between 8 and 25 carbon atoms or mixtures thereof; and

wherein the anti-microbial agent is iodine in a concentration between about 0.1 and about 2.0 percent of the overall composition; and

wherein the ratio of phospholipid to iodine is between about 0.1:1 to about 10:1.

32. A veterinary composition for treating or preventing bovine mastitis comprising:

between about 0.01 and about 20 wt % of a phospholipid compound;

between about 0.1 and 2 wt % iodine as an anti-microbial agent;

an emollient; and

water.

33. The veterinary composition of claim 32 wherein the phospholipid is present in a weight ratio to the anti-microbial agent of between about 1:1 and about 4:1.

34. The veterinary composition of claim 32 wherein the phospholipid is present in a weight ratio to the anti-microbial agent of between about 1.5:1 and about 2.5:1.

35. The veterinary composition of claim 32 wherein the phospholipid is present in a weight ratio to the anti-microbial agent of about 2:1.

36. A method to treat or prevent infection in an animal comprising topically applying to the animal a veterinary

composition comprising an anti-microbial agent and a phospholipid-containing skin conditioner.

37. The method of claim 36 wherein the anti-microbial agent is selected from the group consisting of iodine, quaternary ammonium compounds, chlorine release compounds, peroxides, protonated carboxylic acids, alkylaryl sulfonic acids, chlorine dioxide, and chlorhexidine.

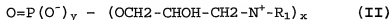
38. A method to treat or prevent bovine mastitis in a lactating cow comprising topically applying to an udder of the cow a veterinary composition comprising an anti-microbial agent and a phospholipid-containing skin conditioner.

39. The method of claim 38 wherein the anti-microbial agent is selected from the group consisting of iodine, quaternary ammonium compounds, chlorine release compounds, peroxides, protonated carboxylic acids, alkylaryl sulfonic acids, chlorine dioxide, and chlorhexidine.

40. The method of claim 38 wherein the veterinary composition comprises between about 0.01 and about 20 wt % phospholipid compound.

41. The method of claim 38 wherein the veterinary composition comprises between about 0.1 and about 2 wt % iodine as the anti-microbial agent.

42. The method of claim 38 wherein the phospholipid is a compound of the formula:



wherein $x + y = 3$ or mixtures thereof; and

wherein R_1 is selected from the group consisting of alkyl, alkylamides, and organosilicone modified alkyl or

alkylamides which contain between 8 and 25 carbon atoms or mixtures thereof.

43. The method of claim 38 wherein the phospholipid is selected from the group consisting of:
linoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, cocoamidopropyl phosphatidylglycerol dimonium chloride phosphate, sunfloweramidopropyl phosphatidylglycerol dimonium chloride phosphate, sodium olivamidopropyl phosphatidylglycerol dimonium chloride phosphate, stearamidopropyl phosphatidylglycerol dimonium chloride phosphate, ricinoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, di-linoleamidopropyl phosphatidylglycerol dimonium chloride phosphate, poly(ethylene glycol)_{n=8} dimethicone sunfloweramidopropyl, phosphatidylglycerol dimonium chloride phosphate complex, dimethicone saffloweramidopropyl phosphatidylglycerol dimonium chloride phosphate complex, sodium grapeseedamidopropyl phosphatidylglycerol dimonium chloride phosphate, and sodium borageamidopropyl phosphatidylglycerol dimonium chloride phosphate.

44. The method of claim 38 wherein the phospholipid is present in a weight ratio to the antimicrobial agent of between about 0.1:1 and about 10:1.

45. The method of claim 38 wherein the phospholipid is present in a weight ratio to the antimicrobial agent of between about 1:1 and about 4:1.

46. The method of claim 38 wherein the phospholipid is present in a weight ratio to the antimicrobial agent of between about 1.5:1 and about 2.5:1.

47. The method of claim 38 wherein the phospholipid is present in a weight ratio to the antimicrobial agent of about 2:1.

48. The method of claim 38 wherein the composition comprises:

between about 0.01 and about 20 wt % of a phospholipid compound;

between about 0.1 and 2 wt % iodine as an anti-microbial agent;

an emollient; and
water.

49. The method of claim 48 wherein the phospholipid is present in a weight ratio to the anti-microbial agent of between about 1:1 and about 4:1.

50. The method of claim 48 wherein the phospholipid is present in a weight ratio to the anti-microbial agent of between about 1.5:1 and about 2.5:1.

51. The method of claim 48 wherein the phospholipid is present in a weight ratio to the anti-microbial agent of about 2:1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/28347

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/00

US CL : 424 /184.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424 /184.1, 512/2, 514/188, 514/78

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
WEST 2.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Agricola

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Cate.ry *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,420,104 A (HOLZNER et al) 30 May 1995, see entire document.	1-29
Y	US 5,945,409 A (CRANDALL et al) 31 August 1999, see entire document.	1-29
Y	US 6,316,428 B1 (CRANDALL et al) 13 November 2001, see entire document.	1-29
Y	EP 0 796 616 B1 (HAYNES, D.) 19 March 1997, see entire document.	1-29
A	US 6,638,978 B1 (KABARA, J.) 28 October 2003, see entire document.	1-29
A	US 5,208,257 B1 (KABARA, J.) 04 May 1993, see entire document.	1-29

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search 12 December 2003 (12.12.2003)	Date of mailing of the international search report 16 AUG 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Khatol Shahman-Silva Telephone No. (703)308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/28347

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-29

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-29 are, drawn to a topical veterinary composition for treatment of infection.

Group II, claim(s) 3-35 are, drawn to a composition for treating bovine mastitis.

Group III, claim(s) 36-51 are, drawn to a method of treating or preventing infection.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical features linking the inventions of groups I-III appears to be a composition containing a phospholipid and an antibacterial agent.

However, Holzner et al. (US Patent NO. 5420104 published May 30 1995) teach a composition containing a phospholipid and an antibacterial agent (see abstract and claim 1)

Therefore, the technical features linking the inventions of groups I-III does not constitute a special technical feature as defined by the PCT Rule 13.2, as it does not define a contribution over the prior art.

The claims are deemed to correspond to the species listed above in the following manner:

The special technical feature of group I is considered to be a topical veterinary composition for treatment of any infection.

The special technical feature of group II is considered to be a composition for treating bovine mastitis.

The special technical feature of group III is considered to be a method of treating or preventing infection.